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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/606,042	06/29/2000	Kenneth B. Ain	50229-194	7670

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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,042	AIN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-14 and 16-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5,7-14 and 16-19* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 2, 2003 has been entered.

2. The amendment filed October 1, 2002 in Paper No. 16 is acknowledged and has been entered. Claims 1 and 16 have been amended.

3. Claims 1-5, 7-14, and 16-19 are pending in the application. Claims 17-19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-5, 7-14, and 16 are currently under prosecution.

Grounds of Claim Rejections Withdrawn

5. Any grounds of rejection set forth in the preceding Office actions that are not specifically reiterated below have been withdrawn.

Claim Objections

6. Claim 4 is objected to because claim 4 recites the limitation "and as a result of administration[,] said response element is re-expressed". The recitation of the limitation renders claim 4 objectionable because claim 1, from which claim 4 depends, recites the imitation "thereby resulting in the expression of the response element", and it is unclear how the recitation of the limitation in claim 4 is intended to further limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 7-14, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing the re-expression of the previously silenced endogenous gene encoding human sodium/iodide symporter in the human thyroid typical papillary carcinoma cell lines, including KAK-5, KAK-10 and NPA'87, and in the human benign follicular adenoma cell line KAK-1, said method comprising a step of administering 5-azacytidine, sodium butyrate, or phenylacetate to the cell line does not reasonably provide enablement for a method for inducing the re-expression of any previously silenced endogenous or exogenous gene encoding a therapeutic response element in any cancerous cell, wherein any demethylating or differentiating agent is administered to the cell for the reasons set forth in the preceding Office actions.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for restoring iodide transport to the thyroid typical papillary carcinoma cell line NPA'87, said method comprising a step of administering 5-azacytidine to transcriptionally activate the expression of a hypermethylated sodium/iodide symporter gene does not reasonably provide enablement for a method for restoring iodide transport to any dedifferentiated thyroid cancer cell, said method comprising a step of administering any demethylating agent to transcriptionally activate the expression of said gene for the reasons set forth in the preceding Office actions.

Applicants have traversed the grounds of these rejections under 35 USC § 112, first paragraph arguing the specification provides an enabling disclosure since several examples are included therein that illustrate the use of the invention.

Applicants' arguments have been carefully considered but in view of the preponderance of evidence have not been found persuasive. For the reasons set forth in the preceding Office actions, the specification is deemed insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention without the need to first perform additional, and an undue amount of experimentation. The factors that have been considered in determining whether undue experimentation would be required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification teaches the invention cannot be used reliably or predictably, and this is perhaps the most significant reason that Applicants' disclosure is regarded as insufficient to meet the enablement requirement set forth under 35 USC § 112, first paragraph. For example, the specification teaches that neither 5-azacytidine, sodium butyrate, nor phenylacetate can be used to restore the expression of the gene encoding the sodium/iodide symporter in every cell line tested. In addition, apparently neither sodium butyrate nor phenylacetate can be used to restore the expression of the gene in follicular carcinoma, and only one or the other, not both of these agents is shown to be capable of restoring expression of the gene in papillary carcinoma. In view of Applicants' disclosure, contrary to Applicants' assertions, the skilled artisan would doubt that the claimed invention could be used with a reasonable expectation of success without the need to perform additional, and an undue amount of experimentation.

Accordingly, Applicants' arguments have again been carefully considered but not found persuasive, and therefore, the rejection of the claims under 35 USC § 112, first paragraph for the reasons set forth in the preceding Office Action is maintained.

9. Claims 1-5 and 7-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method for expressing "a thyroid specific therapeutic response element". However, the specification does not adequately describe the genus of "thyroid specific therapeutic response elements" to meet the written description requirement set forth under 35 USC § 112, first paragraph.

The specification discloses an example in which the expression of a sodium-iodide symporter in cell lines is affected by exposure of the cell lines to an agent, such as 5-azacytidine. Riedel, et al (*Trends in Biochemical Science* **26**: 490-496, 2001) teaches the gene encoding a sodium-iodide symporter is not expressed exclusively by thyroid cells, since the gene is also expressed in mammary tissue, for example. Therefore, a sodium-iodide symporter cannot be representative of the genus of "thyroid specific therapeutic response elements" to which the claims refer.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual

reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Because of the lack of description of at least one representative member of the genus of "thyroid specific therapeutic response elements" to which the claims refer, the disclosure would not reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed. Accordingly, the disclosure is insufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph.

10. The specification is objected to and claim 1 and the claims that depend therefrom are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As amended, claim 1 recites the limitation "other than retinoic acid". However, there does not appear to be proper and sufficient antecedent basis in the specification to support recitation of the limitation in the claims. Accordingly, the recitation of the limitation appears to introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

Furthermore, "other than retinoic acid" appears to be a negative limitation. Adding the expressed exclusion of certain elements implies permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations, in fact, introduce new concepts. See *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983). It is clear that the inclusion of the limitation "other than retinoic acid" is meant to exclude the prior art used as a basis for the rejection of claims under 35 USC §§ 102 and/or 103; however, it is not clear what other subject matter the limitation is meant to exclude, or rather not to exclude.

In addition, Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972). The specification fails to disclose the subgenus of unblocking agents that does not include retinoic acid; therefore, the specification fails to provide proper antecedent basis for the present limitation of subject matter in the claims. For this reason, in view of the amendment to claim 1, the Examiner objects to the specification.

11. Claims 1-5 and 7-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reason set forth in the preceding Office action mailed July 2, 2002.

Claim 1 recites a limitation requiring the therapeutic response element to be "thyroid specific". However, there does not appear to be proper and sufficient

antecedent basis in the specification for recitation of this limitation in the claims. Therefore, the limitation appears to constitute new matter and thereby recitation of the limitation in the claims appears to violate the written description requirement set forth under 35 USC § 112, first paragraph.

As noted in the preceding Office action, this issue might be resolved, however, if Applicants were to point to particular disclosures in the specification that are believed to provide support for recitation of the limitation in the claims.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-5, 7-14, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reason set forth in the preceding Office action.

For the reasons set forth in the Office Action mailed May 9, 2001 (Paper No. 6), the former claims were indefinite because claim 1 and 16 recited the term "tumor specific". Although the present claims recite the term "thyroid specific" rather than "tumor specific", the present claims are indefinite for essentially the same reasons.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Van Herle, et al (*Journal of Clinical Endocrinology and Metabolism* **71**: 755-763, 1990), as evidenced by Schmutzler, et al (*Biochemical and Biophysical Research Communications* **240**: 832-838, 1997).

Schmutzler, et al provides evidence of the inherent effects upon dedifferentiated thyroid cancer cells caused by administering an unblocking agent, namely retinoic acid, to the cells.

Van Herle, et al teach a method for restoring the iodide transport to dedifferentiated human thyroid cancer cells, namely follicular carcinoma, said method comprising a step of administering a demethylating agent, namely retinoic acid, which, as evidenced by the teachings of Schmutzler, et al, causes the re-expression of the previously silenced gene encoding the human sodium/iodide symporter.

The method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an unblocking agent to the same population of cells; thus, the claimed method is anticipated because the method will inherently lead to conferring re-expression of the previously silenced gene encoding the human sodium/iodide symporter and the restoration of iodide transport into the dedifferentiated thyroid cancer cells. *See Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

The prior art agent is deemed to be the same as the agent of the instant claim, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's agent with the agent of the prior art in order to establish that the agent of the prior art does not possess the same material, structural, and functional characteristics of the claimed agent or would not function identically in the claimed method for restoring iodide transport to dedifferentiated thyroid cancer cells. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed probe and primer are functionally different than those taught by the prior art and to establish patentable differences.

In traversing this ground of rejection in Paper No. 16, Applicants have argued that retinoic acid is not a known demethylating agent. Applicants also speculate that retinoic acid may indirectly result in the restoration of iodine transport, but argue that it does not achieve this result by demethylation.

Applicants' arguments have been carefully considered but have not been found persuasive. Despite Applicants' assertion that retinoic acid is not a demethylating agent, there is no factual evidence of record to support the assertion. In addition, claim

16 only requires the agent to be administered in an amount effective to transcriptionally activate a hypermethylated sodium iodide symporter gene; the claim does not require the agent to demethylate the hypermethylated gene, so contrary to Applicants' argument, the mechanism by which retinoic acid directly or indirectly restores iodide transport into the treated cells is not important. As disclosed in the specification, an "unblocking agent", such as retinoic acid, might induce the expression of a transcription factor, which, in turn, might induce the re-expression of the gene encoding the symporter. Therefore, the prior art is still deemed anticipatory of the claimed subject matter, absent a showing of any difference.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 24, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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